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SUMMARY WITH CRITICAL APPRAISAL

Clonidine for the Treatment of Psychiatric Conditions and Symptoms: A Review of Clinical Effectiveness, Safety, and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

Clonidine is an alpha-2 adrenergic receptor agonist which acts in the brain to decrease sympathetic outflow to the heart and peripheral vasculature.[1,2] This has the effect of lowering cardiac output and vascular resistance and clonidine is used to systemically lower blood pressure.[2] Clonidine is a fast-acting antihypertensive medication and its oral formulation typically requires twice daily dosing.[3] In Canada, oral clonidine is indicated for the treatment of hypertension in patients for whom diuretics and beta blockers are ineffective, are contraindicated, or cause adverse effects.[3] It is also indicated for the relief of menopausal flushing.[4]

Aside from antihypertensive effects, clonidine can exert sedative, analgesic, and anxiolytic effects.[5] Therefore, beyond its approved indications, clonidine has been used more recently to treat a variety of psychiatric conditions which include attention deficit hyperactive disorder (ADHD), post-traumatic stress disorder (PTSD), and Tourette syndrome.[2,6,7] There have been case reports of patients abusing clonidine alone[8] or in combination with opioids or benzodiazepines.[8-10] Abuse of clonidine may be related to its above-mentioned effects[10] as well as its reported ability to potentiate and extend opioid-induced euphoria.[8]

Previous CADTH reports pertaining to the management of ADHD[11] and PTSD[12] have identified evidence-based guidelines that suggest clonidine can be used for the treatment of PTSD-associated nightmares and ADHD in adults. A 2013 CADTH report[13] summarizing evidence for the use of clonidine and three other drugs for the treatment of adults with ADHD found no systematic reviews or randomized controlled trials of clonidine in this population. Evidence regarding the use of clonidine for the treatment of adults with psychiatric conditions not restricted to PTSD or ADHD has yet to be summarized in a CADTH report. This report aims to review the clinical effectiveness of and evidence-based guidelines for clonidine for the treatment of adults with psychiatric conditions or symptoms. It also reviews the harms associated with the potential misuse or abuse of clonidine.

Research Questions

1. What is the clinical effectiveness of clonidine for the treatment of adults with psychiatric conditions or symptoms?
2. What are the harms associated with the potential misuse or abuse of clonidine?
3. What are the evidence-based guidelines regarding the use of clonidine for the treatment of psychiatric conditions or symptoms in adults?

Key Findings

Evidence from a retrospective chart review suggested that clonidine may be effective in treating combat nightmares in patients with post-traumatic stress disorder. A retrospective cohort study suggested that addition of clonidine to naltrexone therapy may reduce cigarette smoking and craving in an in-patient opioid detoxification setting. A randomized controlled trial demonstrated that a single dose of clonidine may adversely affect memory

consolidation in patients with major depressive disorder and healthy volunteers. In a retrospective chart review, harms associated with clonidine overdose included impaired consciousness, miosis, hypothermia, bradycardia, hypotension, and severe hypertension and clonidine dose was negatively associated with minimum heart rate. No relevant evidence-based guidelines were identified. The small number of relevant studies identified (n = 4), the lack of large-scale studies (sample sizes of less than 120), and limitations in study design and quality prevented definitive conclusions from being drawn regarding the clinical effectiveness and safety of clonidine for the treatment of adults with psychiatric conditions or symptoms.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, PsycINFO, PubMed, The Cochrane Library, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews (SRs), meta-analyses, randomized controlled trials (RCTs), non-randomized studies, guidelines, and safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and January 17, 2018.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with psychiatric conditions or symptoms (e.g., attention deficit hyperactivity disorder, Tourette syndrome, impulsiveness, stress, sleep disorders, hyperarousal related to post-traumatic stress disorder, non-opioid addictions, borderline personality disorder, and other anxiety disorders)
Intervention	Clonidine
Comparator	Q1: No treatment, placebo, standard of care Q2, Q3: No comparator
Outcomes	Q1: Clinical effectiveness, safety Q2: Misuse or abuse potential, harms Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Results for clonidine used to

treat opioid withdrawal were not reported as a separate CADTH report is planned for this topic. Articles on mixed populations (adult and pediatric) were excluded if they did not report results for the adult population separately.

Critical Appraisal of Individual Studies

The included SRs were critically appraised using the AMSTAR II tool[14] and randomized and non-randomized studies were critically appraised using the Downs and Black checklist.[15] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 370 citations were identified in the literature search. Following screening of titles and abstracts, 353 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, 14 publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are presented by study type in Appendix 2.

1. *What is the clinical effectiveness of clonidine for the treatment of adults with psychiatric conditions or symptoms?*

Study Design

One RCT with a double-blind crossover design[16] and two non-randomized studies[17,18] were identified for this research question. One of the non-randomized studies was a retrospective chart review[17] and one was a retrospective cohort study[18] based on post-hoc analysis of an RCT.

Country of Origin

The identified RCT was conducted in Germany[16] and the retrospective chart review and cohort study were conducted in the US.[17,18]

Patient Population

The RCT studied two separate groups: one group of major depressive disorder (MDD) in-patients and one group of healthy volunteer patients (n = 20 in each group).[16] The cohort study focused on adult in-patients with opioid addiction undergoing methadone-based detoxification who were nicotine-dependent (n = 96).[18] The patients were at a single centre allowing cigarette smoking during the detoxification program.[18] The retrospective chart review studied veterans and active duty soldiers at a single hospital who were diagnosed with PTSD and prescribed medication for combat nightmares associated with PTSD (478

individual patient prescription regimens in 327 patients; 27 prescription regimens with clonidine).[17]

Interventions and Comparators

Patients in the RCT first received a single 0.15 mg dose of clonidine or placebo and then received the other treatment one week later.[16] The retrospective chart review of patients with PTSD combat nightmares included 27 individual prescription regimens or trials of clonidine with dosages ranging from 0.1 mg to 4.0 mg per day and maximum prescription lengths ranging from two to 1216 days.[17] Each trial consisted of medication use at a constant dosage until the dosage was changed or stopped and multiple trials may have been conducted in a one or more patients prescribed clonidine.[17] The other medications and medication combinations prescribed for combat nightmares were: prazosin, terazosin, risperidone, quetiapine, olanzapine, aripiprazole, ziprasidone, perphenazine, trazodone, mirtazapine, prazosin and trazodone, and prazosin and quetiapine.[17] The retrospective cohort study included patients grouped according to whether patients received naltrexone or placebo and whether they received clonidine or not (n = 96).[18] Patients given clonidine received a flexible dose of 0.1 mg to 0.2 mg every six hours.[18]

Outcomes

The RCT studied working memory using a word suppression test with neutral and negative valenced words and tested memory retrieval based on recall of events prior to the day before testing.[16] Working memory and memory retrieval tests were conducted in patients one hour after treatment administration.[16] To test memory consolidation, wordlist learning was performed 15 minutes prior to treatment and word recall was performed 24 hours after treatment.[16] The retrospective chart review on treatment of combat nightmares classified response to treatment as one of the following: no change in combat nightmares (no response), decrease in frequency and severity of combat nightmares (partial response), and total suppression of combat nightmares (full response).[17] The retrospective cohort study evaluated cigarette smoking through cigarette counts by study staff and daily patient smoking diaries.[18] Cigarette craving was assessed through the self-reported Brief Questionnaire of Smoking Urges which consisted of five items describing the rewarding properties of smoking and five items describing relief from negative effects.[18] Both outcomes were measured on each day of the six-day detoxification program.[18]

2. What are the harms associated with the potential misuse or abuse of clonidine?

Study Design

One retrospective chart review was identified.[19]

Country of Origin

The retrospective chart review was conducted in Australia.[19]

Patient Population

The retrospective chart review studied patients over 15 years old admitted to a single hospital toxicology unit for clonidine overdose or poisoning (n = 119).[19]

Interventions and Comparators

The chart review of patients who overdosed on clonidine studied separate groups of patients based on whether clonidine ingestion was acute (n = 108; median dose of 2.1 mg;

range of 0.4 mg to 15 mg) or staggered (n = 11; median dose of 3.6 mg; dose range of 1.5 mg to 30 mg; ingestion period range of 0.5 days to seven days) and whether there were co-ingestants (benzodiazepines, antipsychotics, opioids, anticonvulsants, and alcohol) or not.[19] In patients with acute clonidine ingestion, 40 had ingested clonidine alone and 68 had ingested clonidine with another drug or substance.[19] Out of the 11 patients with staggered clonidine ingestion, 10 ingested another drug.[19]

Outcomes

The retrospective chart review on clonidine overdose studied the following outcomes: bradycardia (heart rate < 60 beats per minute) and its duration, hypotension (systolic blood pressure < 90 mmHg) and its duration, hypertension (systolic blood pressure > 180 mmHg), Glasgow coma score, hypothermia, arrhythmia, death, and administration of and response to antidote treatment (e.g., naloxone or atropine).[19] Associations of clonidine dose with minimum heart rate, minimum systolic blood pressure, and Glasgow coma score were also analyzed.[19]

3. *What are the evidence-based guidelines regarding the use of clonidine for the treatment of psychiatric conditions or symptoms in adults?*

No relevant evidence-based guidelines were identified.

Summary of Critical Appraisal

Additional details regarding the critical appraisal of included publications are presented by study type in Appendix 3.

1. *What is the clinical effectiveness of clonidine for the treatment of adults with psychiatric conditions or symptoms?*

In the RCT,[16] the hypotheses, main outcomes, characteristics of included patients, interventions, and findings were clearly described. Risk of bias from randomization, allocation, blinding, attrition, and selective reporting was low. The memory tests used to measure the outcomes were developed by the authors, with previous publications being cited, and information on the validity and reliability of the tests was not provided. Estimates of random variability and actual *P* values were reported for the main outcomes. The statistical tests were appropriate and post-hoc analyses were clearly identified. Treatment order was not controlled for in the analyses of the outcomes, meaning that factors such as previous test practice during evaluation of the second treatment were not taken into account. Sample size calculations were not provided. Generalizability is limited as a single dose of clonidine is not representative of clonidine treatment in clinical practice. Also, it was unclear whether the included MDD patients and healthy volunteers were representative of their respective source populations as details on recruitment of MDD in-patients were not provided and patients with psychiatric co-morbidities were excluded. Healthy volunteers were recruited through local advertisements without further details given.

The retrospective chart review[17] in patients with combat nightmares clearly described the study objectives, main outcomes, characteristics of included patients, and main findings and the study patients were representative of their source population as all records from patients initially examined during a one year period were assessed for the study criteria. Comparisons between different interventions were not tested. Medication trials were not all independent of one another (multiple trials in some patients) and treatment compliance was not reported. Response to one medication regimen in a patient may have predicted

response to a different dosage or medication in the same patient and differences in treatment compliance between medications may affect observed responses. Response of frequency and severity of combat nightmares to treatment was not assessed using a valid and reliable instrument and estimates of random variability in treatment response were not provided.

In the retrospective cohort study,[18] the main outcomes, characteristics of included patients, and interventions of interest were clearly described. However, the hypotheses and main findings were not clearly described. The post-hoc nature of the study was clearly stated, the outcome measures used were valid and reliable, the statistical tests used to assess the main outcomes were appropriate, and follow-up period was the same for all patients. However, information was not available on principle confounders (such as smoking and smoking cessation history), effect sizes, simple outcome data, random variability of the main outcomes, losses to follow-up, actual *P* values, and statistical power. There was no adjustment for confounding in the analyses. The study patients represented only one centre in the original multi-centre RCT and were originally selected based on opioid addiction rather than nicotine dependence. Also, the staff and facility were not representative of interventions for smoking cessation alone. The results are not generalizable outside of the in-patient opioid detoxification setting.

2. *What are the harms associated with the potential misuse or abuse of clonidine?*

The retrospective chart review[19] clearly described the study objectives, main outcomes, characteristics of included patients, and main findings. The study population was representative of the source population, as all patients admitted over an 18-year period to a single toxicology unit for clonidine overdose or poisoning were included. All analyses were pre-specified in the methods and the outcome measures were valid and reliable. Estimates of random variability were provided for the continuous outcomes but not the dichotomous outcomes. It is unclear whether linear regression analysis was appropriate for testing associations of minimum heart rate, minimum systolic blood pressure, and Glasgow coma score with dose and there was no adjustment for confounders such as underlying medical conditions. Also, ingested doses of clonidine and presence of reported co-ingestants were not confirmed by laboratory analysis.

Summary of Findings

More detailed results from included publications are presented by study type in Appendix 4.

1. *What is the clinical effectiveness of clonidine for the treatment of adults with psychiatric conditions or symptoms?*

One RCT[16] studying the effects of clonidine on memory, one retrospective chart review[17] studying medications for the treatment of combat nightmares in patients with PTSD, and one retrospective cohort study[18] on smoking cessation in patients with opioid addiction undergoing a detoxification program provided information on the clinical effectiveness of clonidine for the treatment of adults with psychiatric conditions or symptoms.

The RCT[16] found that in both healthy volunteer and MDD patients, a single dose of clonidine decreased memory consolidation one day later compared with placebo (approximately 8% to 9% absolute reduction in words recalled; $P = 0.034$) and had no statistically significant effect on working memory and memory retrieval one hour after dosing compared with placebo. The effect size of clonidine versus placebo was not statistically significantly different between the healthy volunteer and MDD patients.

The chart review[17] reported that clonidine was effective in reducing the frequency and/or severity of PTSD combat nightmares in 17 out of the 27 medication trials (63%) evaluated, with dosages ranging from 0.1 mg to 2.0 mg per day. Dosages ranged from 0.1 mg to 4.0 mg per day for patients who reported no response. None of the patients prescribed clonidine achieved full suppression of combat nightmares. Of the six other medications prescribed in 20 or more trials, only risperidone had a higher success rate (51% with partial response and 26% with full response). However, statistical analysis was not performed on the results and there may have been underlying differences between patients prescribed different medications due to the lack of randomization.

The results from the retrospective cohort study[18] suggested that addition of clonidine to the opioid detoxification program for nicotine-dependent patients already taking naltrexone decreased smoking and cigarette craving. Repeated measures ANOVA of the smoking assessment repeated over six days indicated that the clonidine and naltrexone treatment compared with naltrexone alone decreased the number of cigarettes smoked per day ($P < 0.02$) and cigarette craving ($P < 0.01$). Estimates of differences in cigarettes smoked and cigarette craving between patients on naltrexone with and without clonidine treatment were not available. The addition of clonidine to placebo did not have a significant effect on smoking or cigarette craving, indicating that benefits were only observed in patients already receiving naltrexone for opioid withdrawal.

2. *What are the harms associated with the potential misuse or abuse of clonidine?*

One retrospective chart review[19] studied harms associated with the potential misuse or abuse of clonidine. Several outcomes were reported in patients who had been admitted for clonidine overdose. Symptoms of overdose were seen in greater proportions of patients who ingested clonidine alone compared with patients who took a co-ingestant (see Appendix 4 for results broken down by these categories).

The Glasgow coma score was less than the maximum score of 15 in 68% of patients with acute clonidine ingestion and was less than nine in 9% of patients. Patients who took a co-ingestant and had a Glasgow coma score of less than nine had all ingested a benzodiazepine with clonidine. A score of less than 15 indicates a patient unable to perform at least one of the following: spontaneously open eyes, obey verbal commands through motor responses, or appear oriented and converse.[20] A score of less than nine corresponds to a condition serious enough to warrant intubation.[20] The remaining 32% of patients had the maximum score of 15, indicating they were fully awake.

In patients who took clonidine alone, minimum heart rate was significantly associated with clonidine dose, with an effect of –0.002 beats per minute / µg of clonidine (standard error of 0.001, $P = 0.02$). Bradycardia (heart rate < 60 beats per minute) was observed in 76% of patients, with a median duration of 20 hours. Hypotension (systolic blood pressure < 90 mmHg) was reported in 24% of patients, with a later median onset and shorter median duration in patients who took a co-ingestant compared with patients who took clonidine alone. There was no statistically significant association of Glasgow coma score or minimum systolic blood pressure with clonidine dose. Severe hypertension (systolic blood pressure > 180 mmHg) occurred in two patients, both of whom had taken a co-ingestant. Early hypertension was reported in 3% of patients, all of whom took a dose of clonidine (eight to 12 mg) much greater than the median dose of 2.1 mg. A definition for early hypertension was not specified. Miosis was present in 29% of patients and hypothermia was present in 10% of patients.

In terms of interventions for acute overdose, 24% of patients were admitted to the intensive care unit, with 11% of patients being intubated and 22%, 21%, and 7% of patients being treated with activated charcoal, naloxone, and atropine, respectively.

In 11 overdose patients who had taken clonidine in staggered doses, bradycardia was present in 91% of patients, hypotension was present in 27% of patients, and a Glasgow coma score of less than 15 was present in 36% of patients. One patient was admitted to the intensive care unit for cardiac monitoring, two patients were given naloxone, and one patient was given atropine. No arrhythmias or deaths occurred in patients taking either an acute or staggered dose of clonidine.

3. *What are the evidence-based guidelines regarding the use of clonidine for the treatment of psychiatric conditions or symptoms in adults?*

No relevant evidence-based guidelines were identified.

Limitations

Four studies relevant to the use of clonidine for psychiatric conditions or symptoms or the misuse of clonidine in adults were identified and three of the studies had sample sizes of less than 120 patients. The fourth study was a chart review including 327 patients total, with 27 patients or fewer being prescribed clonidine.[17] Also, all of the studies were single centre studies and none were conducted in Canada, limiting the generalizability of the results to the Canadian setting.

The RCT examined the short term (24 hour) effects of a single dose of clonidine, which is not representative of clonidine treatment in clinical practice.

In the chart review of medications for PTSD combat nightmares, compliance with prescribed medication was not reported and multiple medication trials that were conducted within some patients would not have been independent of one another. Statistical comparisons between clonidine and other treatments were not performed. Comparisons would not have been appropriate due to the above-mentioned limitations as well as potential differences among groups of patients prescribed each medication. Study inclusion was limited to veteran and active duty soldiers with combat nightmares and it is unclear whether the results would be relevant for patients with other types of PTSD nightmares.

The retrospective cohort study in smokers undergoing opioid detoxification did not adjust for confounders and did not report effect sizes. The patient sample was not representative of the original study population (opioid withdrawal patients) and the results are only applicable to patients undergoing voluntary smoking cessation and in-patient opioid detoxification simultaneously.

Conclusions and Implications for Decision or Policy Making

A total of four relevant publications were identified, including one RCT,[16] one retrospective cohort study,[18] and two retrospective chart reviews.[17,19] The RCT,[16] retrospective cohort study,[18] and one of the retrospective chart reviews[17] studied the clinical effects of clonidine for the treatment of adults with psychiatric conditions or symptoms. One of the chart reviews studied harms associated with the potential misuse and abuse of clonidine.[19] No relevant evidence-based guidelines were identified. There were no large-scale studies (sample sizes were less than 120) and the small number of relevant studies meant that definitive conclusions could not be drawn.

The evidence for clinical benefits of clonidine treatment was limited by the retrospective nature of two of the relevant studies.[17,18] Clonidine at a dosage of 0.1 mg to 2.0 mg per day may be effective in reducing the frequency and/or severity of PTSD combat nightmares, though statistical comparisons with other medications, placebo, or no treatment were not available.[17] Flexible dose clonidine (0.1 mg to 0.2 mg every six hours) may be effective in reducing cigarettes smoked and smoking craving in nicotine-dependent in-patients undergoing methadone-based opioid detoxification and receiving low-dose naltrexone.[18] However, the effect size was not reported.[18] Memory consolidation may be negatively affected by clonidine, though the single dose studied in the RCT was not representative of clonidine treatment.[16]

Harms observed in clonidine overdose patients included impaired consciousness, miosis, hypothermia, bradycardia, hypotension, and severe hypertension and clonidine dose may be associated with decreased minimum heart rate.[19]

While the use of alpha-2 adrenergic receptor agonists, including clonidine, has been studied in the pediatric population for the treatment of ADHD, tic disorders, and Tourette syndrome,[2,6] none of the identified studies pertained to these conditions in the adult population. One study provided information on harms associated with clonidine overdose,[19] but studies of chronic abuse or misuse of clonidine were not identified.

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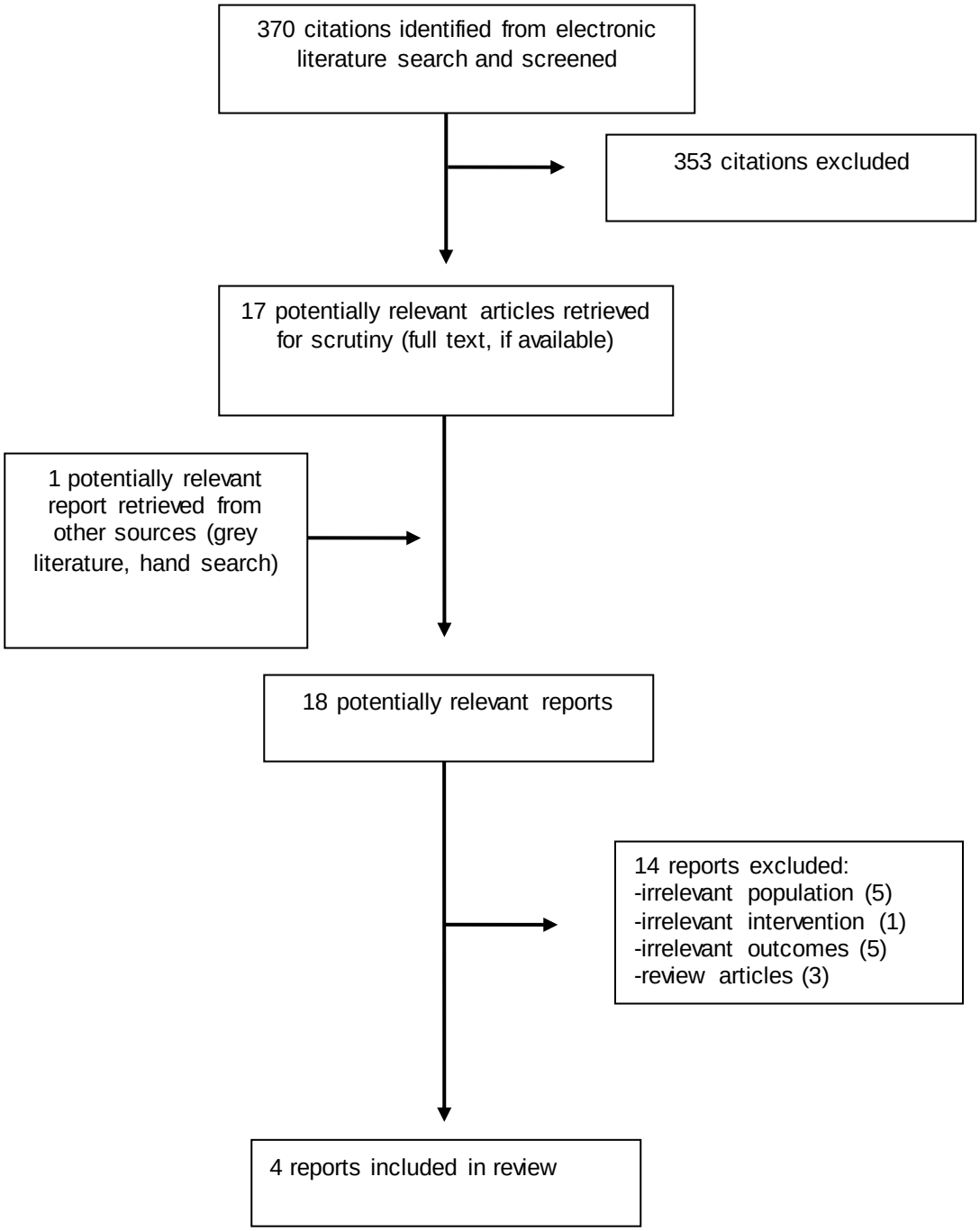
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Randomized Clinical Trial

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Kuffel, 2013, Germany[16]	Double-blind crossover	In-patients with major depressive disorder and age- and gender-matched healthy volunteer patients (n = 20 in each group) Patients with common psychiatric comorbidities were excluded.	Single dose of clonidine hydrochloride 0.15 mg	Single dose of placebo	Memory consolidation, memory retrieval, working memory with either neutral or negative valenced words

Table 3: Characteristics of Included Non-Randomized Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Isbister, 2017, Australia[19]	Retrospective chart review	Patients over 15 years old admitted to a toxicology unit for clonidine overdose or poisoning (N = 119)	Acute ingestion of clonidine alone (n = 40), or with co-ingestants (n = 68), including benzodiazepines, antipsychotics, opioids, anticonvulsants, and alcohol. Median dose of 2.1 mg (range of 0.4 mg to 15 mg). Staggered ingestion of clonidine alone (n = 1) or with co-ingestants (n = 10). Median dose of 3.6 mg (range of 1.5 mg to 30 mg)	N/A	Bradycardia and its duration, hypotension and its duration, early hypertension, severe hypertension, Glasgow coma score, hypothermia, arrhythmia, mortality, administration of and response to antidotes.
Detweiler, 2016, USA[17]	Retrospective chart review	Veteran and active duty soldiers diagnosed with PTSD prescribed medication for	Clonidine with dosages of 0.1 mg to 4.0 mg per day and maximum prescription lengths	Prazosin, terazosin, risperidone, quetiapine, olanzapine,	Frequency and severity of PTSD-related nightmares categorized as: no change in

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
		nightmares associated with PTSD 327 patients and 478 medication trials, including 27 trials with clonidine	of 2 to 1216 days. A medication trial consisted of the use of the medication at the same dosage until the dosage was changed or stopped.	aripiprazole, ziprasidone, perphenazine, trazodone, mirtazapine, prazosin and trazodone, prazosin and quetiapine	nightmares (no response), decrease in frequency and severity of nightmares (partial response), and total suppression of nightmares (full response)
Mannelli, 2013, USA[18]	Retrospective cohort study (post-hoc analysis of an RCT)	Opioid addiction in-patients undergoing methadone-based detoxification at community treatment programs. The studied subgroup of patients was permitted to smoke cigarettes (N = 96).	All patients: 6 day methadone taper Patients who smoked during treatment were divided into four groups based on naltrexone vs. placebo and clonidine vs. no clonidine. Patients on naltrexone received 0.125 mg or 0.25 mg/day. Patients on clonidine received 0.1 mg to 0.2 mg every 6 hours. Naltrexone/clonidine (n = 29) Placebo/clonidine (n = 18)	Naltrexone alone (n = 31) Placebo alone (n = 18)	Mean cigarettes smoked per day, cigarette craving (Brief Questionnaire of Smoking Urges), adverse events

N/A = not applicable; PTSD = post-traumatic stress disorder; RCT = randomized controlled trial.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Randomized Controlled Trial Using the Downs and Black Checklist[15]

Strengths	Limitations
Kuffel et al. 2014[16]	
• The hypotheses, main outcomes, characteristics of included patients, and interventions each group, and findings were clearly described • Estimates of random variability were provided for the main outcomes • There were no patients lost to follow-up • Actual *P* values were reported for the main outcomes • Patients and outcomes assessors were blinded to treatment allocation • Post-hoc analyses were clearly identified • Follow-up length was the same for all patients • Statistical tests used to assess the main outcomes were appropriate • Compliance with the interventions was reliable	• Treatment order was not controlled for in the analyses (crossover study) • It is unclear whether major depressive disorder patients and healthy volunteers asked to participate were representative of their respective source populations • It is unclear whether participants were representative of their respective source populations • Intervention was not representative of clonidine treatment in clinical practice • It is unclear whether the main outcome measures were valid and reliable • It is unclear whether the study had sufficient power to detect differences between treatment groups

Table 5: Strengths and Limitations of Non-Randomized Studies Using the Downs and Black Checklist[15]

Strengths	Limitations
Isbister et al. 2017[19]	
• The objective of the study, main outcomes to be measured, characteristics of the included patients, and main findings were clearly described • Estimates of random variability were provided for continuous outcomes • Study patients were representative of patients admitted to a single hospital for clonidine overdose or poisoning • All analyses were pre-specified in the methods section • Main outcome measures were valid and reliable	• Estimates of random variability in dichotomous outcomes were not provided • Actual *P* values were not reported for all linear regression analyses • Unclear whether linear regression analysis was appropriate for associations with dose • Linear regression analysis did not adjust for confounders
Detweiler et al. 2016[17]	
• The objective of the study, main outcome to be measured, characteristics of the included patients, and main findings were clearly described • Study patients were representative of veterans and active duty soldiers prescribed medication for PTSD combat nightmares at a single centre	• Estimates of random variability were not provided for the main outcome • Adverse events were not reported • Retrospective chart review without a control group or statistical analyses • Some patients underwent more than one medication trial; trials were not independent of one another • Treatment compliance was not reported • Treatment response was not assessed using a valid and reliable instrument

Strengths	Limitations
Mannelli et al. 2013[18]	
• The main outcomes to be measured, characteristics of included patients, and interventions of interest were clearly described • Adverse events were assessed (no list provided) • The post-hoc nature of the analysis was clearly stated • Follow-up period was the same for all patients • Statistical tests used to assess the main outcomes were appropriate • Main outcome measures used were valid and reliable • Patients were recruited from the same population and were in different intervention groups	• The hypotheses of the study and main finding were not clearly described • A list of principal confounders was not provided • Effect sizes and simple outcome data were not reported • Estimates of random variability were not provided for the main outcomes • Numbers and characteristics of patients lost to follow-up was not described for each group • Actual *P* values were not reported • Study patients were not representative of patients in the original study as they represented only one centre • The staff and facility are not representative of treatment for smoking cessation alone (but may be representative of treatment for opioid addiction) • There was not adequate adjustment for confounding in the analyses • It is unclear whether the study had sufficient power to detect differences between treatment groups

PTSD = post-traumatic stress disorder.

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Randomized Controlled Trial

Main Study Findings	Author's Conclusion
Kuffel et al. 2014[16]	
MDD and Healthy Volunteer Patients (n = 20 in each group) • Memory consolidation: ○ Significantly decreased with clonidine vs. placebo in all patients; *P* = 0.034 for main effect; *P* = 0.04 when adjusted for word valence ○ Mean percentage of words recalled, estimated from a graph ▪ Approximately 54% vs. 62% for clonidine vs. placebo in healthy volunteer patients ▪ Approximately 52% vs. 61% for clonidine vs. placebo in MDD patients ○ Clonidine vs. placebo effect was not significantly different between MDD patients and healthy volunteers; *P* = 0.76 for MDD patients vs. healthy volunteers; *P* = 0.85 for the interaction • Memory retrieval: ○ No significant difference with clonidine vs. placebo in all patients; *P* = 0.78 for main effect ○ No significant difference for MDD patients vs. healthy volunteers; *P* = 0.37 for the main effect; *P* = 0.93 for the interaction • Working memory: ○ No significant difference in neutral test with clonidine vs. placebo in all patients; *P* = 0.92 for the main effect ○ No significant difference in neutral test for MDD patients vs. healthy volunteers; *P* = 0.37 for the main effect and interaction ○ No significant difference in negative test with clonidine vs. placebo in all patients; *P* = 0.50 for the main effect ○ No significant difference in negative test for MDD patients vs. healthy volunteers; *P* = 0.28 for the main effect; *P* = 0.30 for the interaction	*"Noradrenergic blockade significantly impaired memory consolidation across the entire sample. However, there was no difference between depressed patients and controls."* p. 90

MDD = major depressive disorder.

Table 7: Summary of Findings of Included Non-Randomized Studies

Main Study Findings	Author's Conclusion
Isbister et al. 2017[19]	
Acute Clonidine Ingestion (n = 108) • GCS (maximum score of 15 indicates a fully awake patient): ○ GCS < 15 in 73 patients (68%) ▪ Clonidine alone: 22 patients (55%) ▪ Clonidine with co-ingestant: 51 patients (75%) ○ No significant association with dose (*P* = 0.40) ○ Coma (GCS < 9) in 10 patients (9%) ▪ Clonidine alone: 2 patients (5%) ▪ Clonidine with co-ingestant:8 patients (12%); all cases included at least a benzodiazepine • Miosis in 31 (29%) patients: ○ Clonidine alone: 10 patients (25%) ○ Clonidine with co-ingestant: 21 patients (31%) • Hypothermia (temperature < 35°C) in 11 patients (10%) • Minimum heart rate (HR): ○ Median of 48 bpm (IQR of 40 to 57 bpm) ▪ Clonidine alone: 48 bpm (40 to 62 bpm) ▪ Clonidine with co-ingestant: 47 bpm (40 to 55 bpm) ○ Range of 32 to 88 bpm ○ Significantly associated with clonidine alone dose; slope of –0.002 ± 0.001 bpm/µg; *P* = 0.02 • Sinus bradycardia (HR < 60 bpm): ○ 82 patients (76%): ▪ Clonidine alone: 27 patients (68%) ▪ Clonidine with co-ingestant: 55 patients (81%) ○ Median onset of 2.5 hours post-ingestion ○ Median duration of 20 hours ○ 41% with bradycardia were discharged still bradycardic • Minimum systolic blood pressure (BP): ○ Median of 96 mmHg ○ No significant association with dose (*P* value not reported) • Hypotension (systolic BP < 90 mmHg): ○ 26 patients (24%) ○ Clonidine alone: ▪ 10 patients (25%) ▪ Median onset of 4.2 hours ▪ Median duration of 11 hours ○ Clonidine with co-ingestant: ▪ 16 patients (24%) ▪ Median onset of 8 hours ▪ Median duration of 2.8 hours • Severe hypertension (systolic BP > 180 mmHg) in 2 patients (2%); both patients took co-ingestant • Early hypertension (not defined) in 3 patients (3%) with	*"Our study found that clonidine causes persistent but not life-threatening clinical effects including bradycardia and CNS [central nervous system] depression. Although these initially appear to be clinically significant, they are unlikely to predict a poor patient outcome."* p. 191 *"Bradycardia was significantly associated with the dose ingested in the clonidine alone overdoses, and developed within hours of ingestion in both clonidine alone and clonidine with co-ingestant overdoses. Bradycardia lasted for 24 to 48 h [hours] and was the same for clonidine alone and clonidine with co-ingestant overdoses. In contrast, hypotension was not dose-related, had a later and far more variable onset and variable duration. The onset and duration of hypotension was also different between clonidine alone and clonidine with co-ingestant overdoses."* p. 190-191

Main Study Findings	Author's Conclusion
clonidine doses of 8, 10, and 12 mg • No arrhythmias or deaths • 26 patients (24%) admitted to ICU • Intubation and ventilation: ○ 12 patients (11%) ○ Clonidine alone: ▪ 2 patients (5%) ▪ 5 mg dose in one case; aggression in other case ○ Clonidine with co-ingestant: ▪ 10 patients (15%) ▪ 6 patients (9%) in coma • Treatment: ○ Activated charcoal in 24 patients (22%) ○ Naloxone in 23 patients (21%) ○ Atropine in 8 patients (7%) ○ Clonidine alone: ▪ Activated charcoal in 10 patients (25%) ▪ Naloxone in 7 patients (18%) ▪ Atropine in 4 patients (10%) ○ Clonidine with co-ingestant: ▪ Activated charcoal in 14 patients (21%) ▪ Naloxone in 16 patients (24%) ▪ Atropine in 4 patients (6%) **Staggered Clonidine Ingestions (n = 11)** • Bradycardia (HR < 60 bpm) in 10 patients (91%) • Hypotension (systolic BP < 90 mmHg) in 3 patients (27%) • GCS < 15 in 4 patients (36%) • No arrhythmias or deaths • 1 (9%) patient admitted to ICU for cardiac monitoring • Naloxone treatment in 2 patients (18%) • Atropine treatment in 1 patient (9%)	
Detweiler et al. 2016[17]	
No response (no change in combat nightmares), partial response (decrease in frequency and severity of combat nightmares), and full response (total suppression of combat nightmares) to medications prescribed for PTSD combat nightmares: Clonidine (27 medication trials): • No response in 10 trials (37%); dosages of 0.1 to 4 mg/day • Partial response in 17 trials (63%); dosages of 0.1 to 2 mg/day • No patients had a full response Prazosin (106 medication trials): • No response in 54 trials (51%); dosages of 1 to 20 mg/day • Partial response in 46 trials (43%); dosages of 1 to 10 mg/day • Full response in 6 trials (6%); dosages of 1 to 10 mg/day Risperidone (81 medication trials): • No response in 19 trials (23%); dosages of 0.25 to 5 mg/day • Partial response in 41 trials (51%); dosages of 0.5 to 6 mg/day	*"The findings of this comparative study strongly suggest the need for additional investigation of multiple medications. In addition, the positive results for risperidone at this VA [Veterans Affairs] could suggest its use as the first treatment choice for PTSD [post-traumatic stress disorder] nightmares, since positive results occur rapidly at a limited dose range. However, this choice would need to be weighed against the only moderately less successful clonidine and terazosin and their lower risk of adverse effects. Further study of this option is warranted."* p. 20

Main Study Findings	Author's Conclusion
• Full response in 21 trials (26%); dosages of 0.5 to 3 mg/day Quetiapine (72 medication trials): • No response in 36 trials (50%); dosages of 12.5 to 500 mg/day • Partial response in 30 trials (42%); dosages of 25 to 800 mg/day • Full response in 6 trials (8%); dosages of 6 to 287 mg/day Terazosin (26 medication trials): • No response in 10 trials (39%); dosages of 1 to 20 mg/day • Partial response in 16 trials (61%); dosages of 2 to 50 mg/day • No patients had a full response Trazodone (22 medication trials): • No response in 14 trials (64%); dosages of 50 to 200 mg/day • Partial response in 7 trials (32%); dosages of 50 to 300 mg/day • Full response in 1 trial (4%); dosage of 200 mg/day Mirtazapine (20 medication trials): • No response in 10 trials (50%); dosages of 7.7 to 30 mg/day • Partial response in 9 trials (45%); dosages of 7.5 to 30 mg/day • Full response in 1 trial (5%); dosage of 15 mg/day Olanzapine, aripiprazole, ziprasidone, perphenazine, prazosin and trazodone, and prazosin and quetiapine were prescribed in ≤ 5 trials.	
Mannelli et al. 2013[18]	
Nicotine-Dependent In-Patients of an Opioid Detoxification Program (N = 96) • Smoking (cigarettes/day) was significantly reduced in naltrexone/clonidine group vs. naltrexone alone group; $P < 0.02$ • Probability of smoking less than the daily average was not significantly higher in placebo/clonidine group vs. placebo alone group; RR = 1.2; $P = 0.5$ • Cigarette craving: ○ Significantly reduced in naltrexone/clonidine group vs. naltrexone alone group; $P < 0.01$ ○ Not significantly reduced in placebo/clonidine group vs. placebo alone group; $P < 0.13$ ○ "Positive" craving item scores were significantly reduced in naltrexone/clonidine group vs. naltrexone alone group (P < 0.03), indicating less craving associated with the rewarding properties of smoking ○ "Negative" craving item scores were significantly reduced in naltrexone/clonidine group vs. naltrexone alone group (P < 0.03), indicating less craving associated with relief from negative effects • No medication-related adverse events	*"Despite its limitations, this study suggests that VLNTX [very low dose naltrexone] + low dose clonidine is well tolerated and associated with improved smoking behaviors in OA [opioid addiction]. Further investigations should test the effectiveness of this pharmacological combination for smoking cessation in patients with or without comorbid substance abuse disorders."* p. 1711

BP = blood pressure; bpm = beats per minute; GCS = Glasgow coma score; HR = heart rate; ICU = intensive care unit; PTSD = post-traumatic stress disorder; RR = risk ratio.

Appendix 5: Additional References of Potential Interest

Case Reports

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Pomerleau AC, Gooden CE, Fantz CR, Morgan BW. Dermal exposure to a compounded pain cream resulting in severely elevated clonidine concentration. J Med Toxicol. 2014 Mar;10(1):61-4. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24129834

Schindler EAD, Tirado-Morales DJ, Kushon D. Clonidine abuse in a methadone-maintained, clonazepam-abusing patient. J Addict Med. 2013;7(3):218-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23519051

Irrelevant Outcomes

Tamburello AC, Kathpal A, Reeves R. Characteristics of inmates who misuse prescription medication. J Correct Health Care. 2017;23(4):449-58. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28884614

Gahr M, Freudenmann RW, Eller J, Schonfeldt-Lecuona C. Abuse liability of centrally acting non-opioid analgesics and muscle relaxants--a brief update based on a comparison of pharmacovigilance data and evidence from the literature. Int J Neuropsychopharmcol. 2014 Jun;17(6):957-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24552880